Abstract in English

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Title of Thesis: : Determination of the stoichiometric ratio of iron chelators by Job's method

Iron is an important biogenic element affecting many biochemical reactions in the body. Its deficiency and excess cause pathophysiological changes in the organism. Excess of iron is very often the result of frequent blood transfusions in the treatment of hematologic diseases. It may also occur in iron metabolism disorders (chronic intoxication). Acute intoxication after ingestion of excessive amounts of iron is life threatening especially in children.

Chelators are used to remove excess iron from the body. It is a heterogeneous group of substances capable of binding iron. Standard drug of this group is parenterally administered deferoxamine. Oral chelators (deferiprone, deferasirox) are also currently used. Other indications of these substances are now the subject of research, which investigates their potential benefits in cancer therapy and acute myocardial infarction. The pH changes play an important role in the pathogenesis of both mentioned conditions.

In this work, the stoichiometric ratios of complexes of selected chelators (deferoxamine, deferiprone, deferasirox, H2QPyQ /2,6-bis[4(1-phenyl-3-methylpyrazol-5-one)carbonyl]pyridine/) were determined spectrophotometrically with divalent and trivalent iron in various pathophysiologically relevant pHs (4.5, 5.5,6.8 and 7.5) using the standard Job's method.

From the tested compounds, deferoxamine formed with ferrous and ferric ions at all tested pH complexes with stoichiometry 1:1, although in some cases, the method revealed a complex with unexpected 3:4 stoichiometry (0.75:1). Another studied drug was H2QPyQ. This substance did not form complexes with ferrous ions or had low affinity to ferrous ions. Although a complex with ferric ions was formed at pH 4.5, this method did not allow to determine the exact stoichiometry. At pH 5.5

a complex with a ratio 2:1 was formed. At higher pHs the substance had again low affinity to ferric ions. The compound deferiprone formed complexes with ferrous / ferric ions in the ratio 3:1 with exception of pH 4.5 and ferrous ions, where it was not possible to determine the stoichiometry . Deferasirox formed complexes with ferrous and ferric ions in the ratio 2:1 at pH 5.5, 6.8 and 7.5. At pH 4.5, only an insignificant shift in the absorption maxima was found after addition of ferrous ions, a complex with 1:1 stoichiometry was found in the case of ferric ions.

In conclusion, the pH is an important factor in the formation of complexes of ferrous or ferric ions with the tested chelators.